

# Pharmacological similarities and differences between $\beta_2$ -agonists

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**Abstract** Formoterol and salmeterol are both long-acting bronchodilators that are effective in the treatment of asthma. However, some differences exist in their pharmacology that are reflected in their clinical profiles. Formoterol has a rapid onset of action, whereas salmeterol causes bronchodilation in a somewhat slower manner. However, both of these drugs are long-acting. After single doses clear effects are maintained for 12 h after inhalation, and with high doses effects are observed even at 24 h. Differences between the maximal effects of both drugs are also a consequence of their pharmacological properties. Thus, formoterol has higher intrinsic activity than salmeterol, which means that it is a full agonist, whereas salmeterol is a partial agonist on the  $\beta_2$ -receptor. Physicochemical properties of the drugs may explain the differences in onset and duration of action. Adequate water solubility and moderate lipophilicity of formoterol ensures rapid diffusion to the  $\beta_2$ -receptor on the smooth muscle and rapid bronchodilating activity. Salmeterol, on the other hand, may diffuse more slowly to the  $\beta_2$ -receptor because of its high lipophilicity, explaining the slower onset of action. Unlike salbutamol, which is hydrophilic and has a rapid onset and short duration of action, both formoterol and salmeterol possess adequate lipophilic properties to remain in the airway tissues as a depot in close vicinity to the  $\beta_2$ -receptor, explaining their long duration of effect. The long duration of salmeterol has also been suggested to depend on an anchored binding within the  $\beta_2$ -receptor (1). The pharmacological evidence for a rapid onset of action of formoterol, but long duration of effect, is supported by several clinical studies. The fast onset of bronchodilation and high intrinsic activity of formoterol therefore suggest that it can be used for relief treatment in patients with asthma if they are concomitantly treated with inhaled glucocorticoids.

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## INTRODUCTION

Formoterol and salmeterol are both long-acting  $\beta_2$ -adrenoceptor agonists ( $\beta_2$ -agonists), but their pharmacological and clinical profiles differ in several ways (Table 1) (2). In particular, formoterol has a rapid onset of action (within minutes), whereas salmeterol causes bronchodilation more slowly. Salbutamol and terbutaline are  $\beta_2$ -agonists with rapid onset, but a much shorter duration of action than both salmeterol and formoterol. Chemical differences, affecting the tissue diffusion rates and how they interact with the  $\beta_2$ -receptor, may explain these variations in properties.

Following inhalation, all asthma drugs are deposited on the mucosal lining fluid. After dissolving in this liquid layer, they diffuse through the different tissue components deeper into the bronchial wall. The most impor-

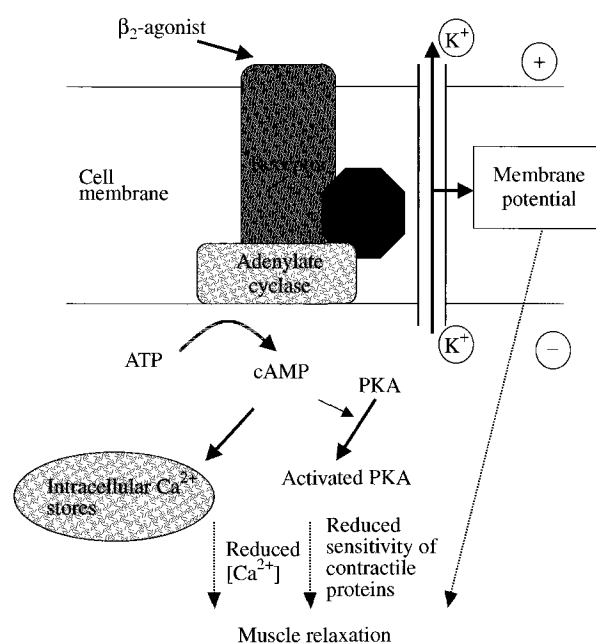
tant target of  $\beta_2$ -agonists are  $\beta_2$ -adrenoceptors in smooth muscle. Binding to the receptor initiates a cascade of intracellular biochemical events that ultimately cause bronchodilation (Fig. 1). Briefly, coupling of the  $\beta_2$ -adrenoceptor, through the Gs protein  $\alpha$  subunit ( $G_s\alpha$ ), to adenylate cyclase results in an increase in intracellular cyclic AMP (cAMP) which leads to protein kinase A being activated. Activated protein kinase A inhibits phosphorylation of key muscle proteins involved in the control of smooth muscle tone; cAMP also results in inhibition of calcium ion release from intracellular stores. Together, these events lead to a general relaxatory effect of the airway smooth muscle; cAMP-independent mechanisms may also be involved in the relaxant response and these may involve direct interaction of  $G_s\alpha$  with potassium channels that are present in the smooth muscle cell membrane (3).

The degree of the bronchodilatory response of a  $\beta_2$ -agonist is related to the concentration of drug in the vicinity of the smooth muscle cells and the degree of activation of the receptor by the  $\beta_2$ -agonist. The onset of

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**Table 1.** Pharmacological and clinical profiles of salbutamol, formoterol and salmeterol

	Salbutamol	Formoterol	Salmeterol
Selectivity $\beta_2$ -adrenoreceptor ( $\beta_2/\beta_1$ ratio of inhibition constants) <sup>a</sup>	Moderately high (13)	High (60)	Very high (190)
Receptor binding affinity ( $pK_i$ ) <sup>a</sup>	High (5.83)	High (8.10)	High (7.97)
Onset of action	Fast	Fast	Slow
Duration of bronchodilatory effect	Short	Long	Long
Agonist activity	Full agonist	Full agonist	Partial agonist
Lipid solubility	Low	Moderate	High

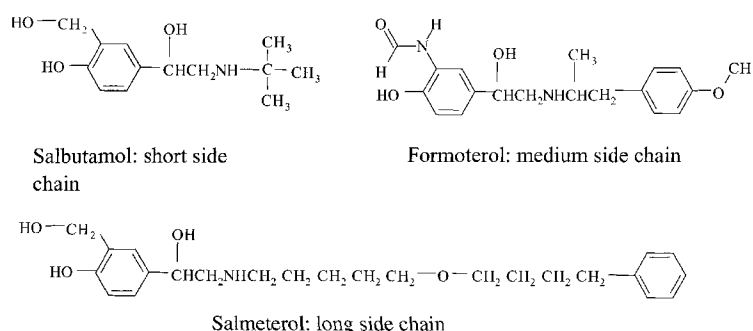
<sup>a</sup>From Roux *et al.* (2)**Figure 1.** Biochemical mechanisms involved in smooth muscle relaxation following  $\beta_2$ -adrenoceptor activation. cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; ATP: adenosine triphosphate.

bronchodilation and the duration of effect of an inhaled drug are influenced by the time it takes for effective concentrations of the drug to be reached and maintained at the receptor site.

## RECEPTOR INTERACTION

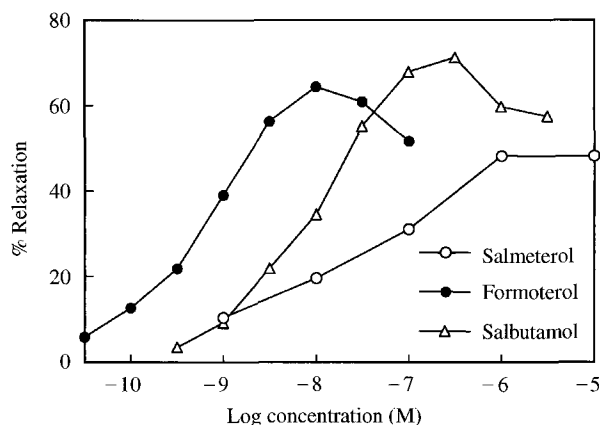
Formoterol, salmeterol, salbutamol and terbutaline have clear differences in their chemical structure, consequently their interaction with  $\beta_2$ -receptors may differ to some extent. Subtle variations in the electrochemical shape of their head groups (Fig. 2) affect the strength of the interaction between the agonist and receptor and, therefore, influence the degree of signal transduction.

Formoterol has additional methoxy groups in the side chain, which enables the drug to bind to the receptor with high affinity and leads to efficient signal transduction (2,4). By contrast, salmeterol does not change the shape of the receptor to such a degree that full signal transduction is achieved. Salmeterol is, therefore, a partial agonist in relation to formoterol, which explains the lesser degree of maximal dilatation by salmeterol of severely contracted tracheobronchial smooth muscle (5,6) (Fig. 3).

**Figure 2.** Chemical structures of formoterol, salmeterol and salbutamol.

## ONSET OF ACTION AND DURATION OF EFFECT

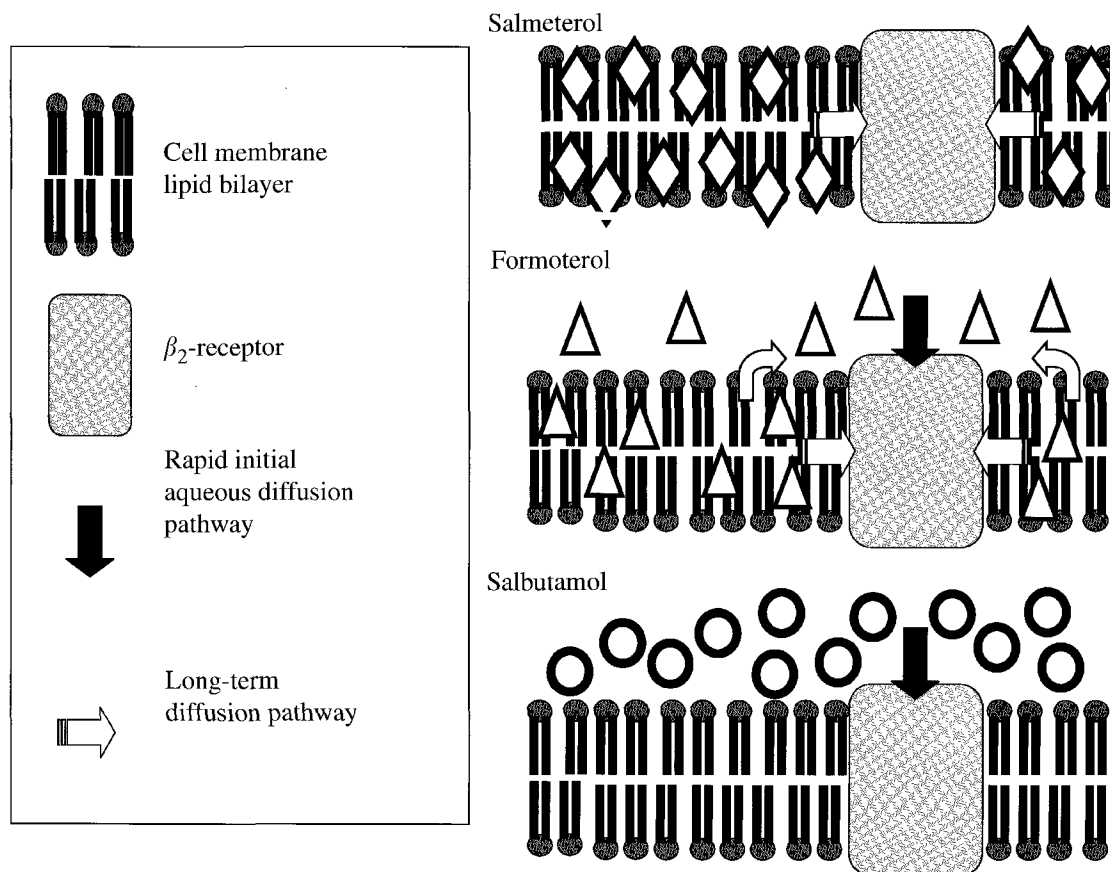
The mechanism for the long duration of action of inhaled salmeterol and formoterol has been debated. Some data from cell molecular experiments, showed that some very



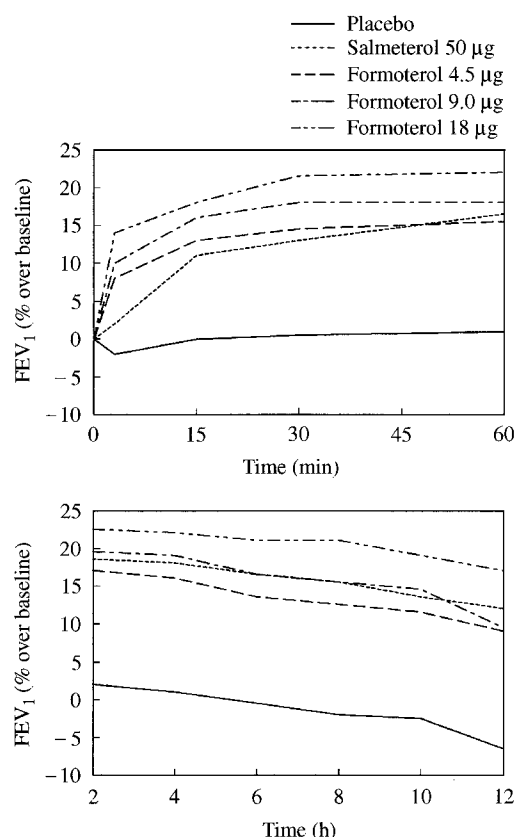
**Figure 3.** Cumulative dose-response curves of formoterol, salmeterol and salbutamol in severely constricted (carbachol 3  $\mu$ M) isolated guinea pig trachea. As can be seen in the figure, formoterol causes a greater bronchodilation than salmeterol (5).

specific mutations of the  $\beta_2$ -receptor caused loss of the long duration of action of salmeterol, but not formoterol, and it was, therefore, suggested that anchored binding of salmeterol within the  $\beta_2$ -receptor was responsible for its long duration of action (1). This explanation may be valid for salmeterol, but anchored binding does not explain the long-lasting effects of formoterol. It was therefore suggested by Anderson (7) that the lipophilicity of formoterol and salmeterol may be responsible for their long duration of action. Both formoterol and salmeterol have sufficient lipophilicity to enter and be stored in any cell membranes, which in the airways would allow these drugs to be accessible to  $\beta_2$ -receptors on the bronchial smooth muscle for a prolonged period of time (Fig. 4).  $\beta_2$ -agonists with greater water solubility, such as salbutamol and terbutaline, diffuse more readily through the tissue, but are also washed away more rapidly.

As well as explaining differences in the duration of action of salmeterol and formoterol, lipophilic characteristics may also explain differences in their onset of action. Although both salmeterol and formoterol partition into lipid regions of bronchial tissues and cell membranes, the intermediate lipophilicity of formoterol means that a far higher proportion of formoterol is retained in the extra-cellular space. The result is a rapid diffusion of formoterol to  $\beta_2$ -receptors and a fast onset of effect. Salmeterol



**Figure 4.** Membrane and receptor interaction of salbutamol, salmeterol and formoterol: the microdiffusion theory.



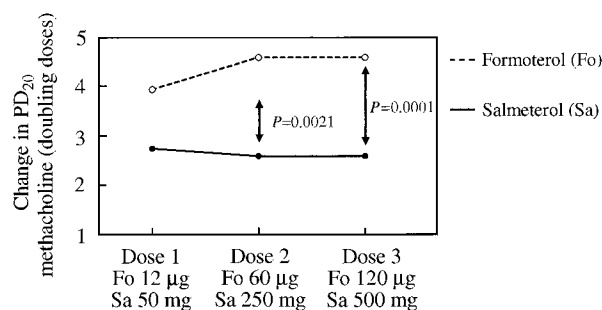
**Figure 5.** Comparative bronchodilating effects of salmeterol and formoterol (8).

diffuses more slowly through lipid regions and its onset of action is delayed.

## CLINICAL PROFILES

The clinical relevance of differences in the pharmacological profiles of salmeterol and formoterol has been confirmed in a double-blind, crossover, clinical study in asthma conducted by Palmqvist *et al.* (8). Both drugs showed a bronchodilating effect lasting more than 12 h, but formoterol showed a more rapid onset of action (Fig. 5). The rapid onset of action of formoterol is, in fact, similar to that of salbutamol (9). This could explain why formoterol, and not salmeterol, has been documented as an effective reliever medication in asthma (10).

*In vitro* data also show that formoterol has a higher pharmacological efficacy than salmeterol (5) but until recently this had not been demonstrated in the clinical situation. However, it has now been shown that formoterol has a higher efficacy than salmeterol in protecting against methacholine provocation in asthma patients (11) (Fig. 6). This study supports the view that formoterol has dose-dependent effects and that additional effects are achieved if the dose of formoterol is increased.



**Figure 6.** Bronchoprotection offered by salmeterol and formoterol against methacholine provocation (11). PD<sub>20</sub>: provocative dose producing a 20% fall in FEV<sub>1</sub>.

A more rapid onset of systemic side effects with formoterol, in comparison with salmeterol, is expected in line with its rapid onset of action and high efficacy. This was indeed found in the previous study evaluating airway efficacy (11), and has been confirmed in a recent dose-response study in healthy volunteers (12). Both salmeterol and formoterol caused an early dose-dependent increase in heart rate and glucose concentration and a fall in diastolic blood pressure and plasma potassium concentration. Formoterol also caused an early increase in systolic blood pressure. The cardiovascular effects occurred more rapidly than the metabolic effects and the response to formoterol was faster, apart from the glycaemic response, than that of salmeterol. However, the effects of salmeterol in general were more prolonged. These results are in line with the recent report that formoterol has a similar duration of systemic effects to traditional short-acting  $\beta_2$ -agonists such as salbutamol (13). Both healthy subjects and asthmatic patients were evaluated and the systemic responses were more pronounced in the healthy subjects than in the asthmatics, which is probably the result of induced tolerance to the systemic effects during regular formoterol treatment. Importantly, the reduction in serum potassium levels, a surrogate marker for systemic side effects, was not prolonged with formoterol when compared with an equieffective concentration of salbutamol. This confirms earlier data showing that formoterol at higher doses is not long acting in terms of serum potassium and electrocardiographic changes compared with terbutaline (14). In practice, systemic side effects are seldom a problem with formoterol.

## CONCLUSIONS

Differences in the pharmacological properties of formoterol and salmeterol are reflected to a large extent in their clinical profiles. Thus, formoterol has a higher efficacy than salmeterol in both bronchial smooth muscle systems *in vitro*, as well as in asthmatic patients *in vivo*.

This suggests that formoterol will have additive effects in the airways when the dose is increased and may, therefore, in the future, be recommended for the treatment of acute asthma (15). This possibility is further supported by the rapid onset of action of formoterol (8,9). Formoterol has recently, in a large multicentre study, been shown to be suitable for as-needed relief medication in asthmatic patients treated with inhaled glucocorticoids (10).

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